Nucleotide Sequence Disclosure

On page 2 of the Office Action, the Examiner indicated that there were sequences presented in the application that did not include SEQ ID NOs (particularly, in Fig. 1). In response, applicant has enclosed a proposed drawing correction which adds the SEQ ID NOs to Fig. 1A and Fig. 1B. Additionally, and in compliance with the sequence rules, applicant has enclosed the following:

1. A computer readable form (CRF) copy of a replacement Sequence Listing in the form of a 3 1/2" diskette;
2. A paper copy of the replacement Sequence Listing, replacement pages 1-28; and
3. A statement that the content of the paper and computer readable form are the same and include no new matter.

Applicant respectfully requests that the Sequence Listing be entered in the specification and maintains that the application now complies with the sequence rules.

Restriction Requirement

On pages 2-23 of the Office Action, the Examiner required restriction to one of the following allegedly separate and distinct inventions:

I.	Claims 1-7, 20-24, and 29	Nucleic acids encoding T-type calcium channel, cells and vectors comprising the nucleic acids, and methods for increasing expression of T-type calcium channel using the nucleic acids

II.	Claims 8-13	Antisense nucleic acids, cells and vectors comprising the antisense nucleic acids, and methods for decreasing expression of T-type calcium channel using the antisense nucleic acids
III.	Claims 14-19	Ribozymes, cells and vectors comprising the ribozymes, and methods for decreasing expression of T-type calcium channel using the ribozymes
IV.	Claims 25-26	Methods for screening a substance for its ability to modify T-type calcium channel function
V.	Claims 27-28	Method for obtaining DNA encoding T-type calcium channel
VI.	Claims 30-32	Oligomers capable of hybridizing to nucleic acids encoding T-type calcium channel
VII.	Claims 33-36 and 40	T-type calcium channel protein and compositions containing same
VIII.	Claims 37-39 and 41-42	Antibodies to T-type calcium channel protein and use thereof to detect for the presence of T-type calcium channel protein
IX.	Claims 43-49	Method of modifying insulin secretion
X.	Claims 50-55	Method of treating diabetes

XI.	Claim 56	Method of modifying basal calcium levels in cells
XII.	Claim 57	Method of modifying action potential of L-type calcium channels
XIII.	Claim 58	Method of modifying pancreatic beta cell death
XIV.	Claim 59	Method of modifying pancreatic beta cell proliferation
XV.	Claims 60	Method of modifying calcium influx through L-type calcium channels

In response to the restriction requirement, applicant hereby affirms the election of Group IX, claims 43-49, for prosecution at this time.

35 U.S.C. §112, first paragraph, Rejection

On pages 23-26 of the Office Action, the Examiner rejected claims 43-49 under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The Examiner alleged that "the specification, while being enabling for modifying beta cell insulin secretion using known calcium channel blockers, does not reasonably provide enablement for modifying beta cell insulin secretion using any calcium channel blocker or inhibitor of channel formation, ribozyme, antisense or an expressed gene in vivo." The Examiner cites Verma et al. for teaching that "modifying insulin secretion in beta cells in vivo (whole organism) via calcium channel blockers was unpredictable ... calcium channel blockers reported to inhibit insulin secretion in vitro do not predictably produce the same effect in vivo."

In response to this rejection, applicant points out that the claims herein are based on the discovery of the direct

relationship between functioning T-type calcium channels in pancreatic beta cells and insulin secretion in those pancreatic beta cells. The data presented in the specification clearly shows this connection. The claims are specifically directed to modifying insulin secretion **by pancreatic beta cells** by modifying levels of functional T type calcium channels **in the pancreatic beta cells**. The Examiner's rejection and recitation of Verma et al. for the teaching that in vitro blockers do not always work in vivo is not in accordance with the claim language. The claim language specifies that in the event that levels of functional T type calcium channels **in the pancreatic beta cells** are modified, insulin secretion **by those pancreatic beta cells** will be modified. The particular method of modifying is not relevant. The issues regarding administration of antisense or other inhibitors, and whether those inhibitors work in vitro or in vivo, is not relevant. The claims state that if levels of functional T type calcium channels **in the pancreatic beta cells** are modified, insulin secretion **by those pancreatic beta cells** will be modified. This will always be true. Applicant has found this discovery, and should not be required to limit the concept claimed to any particular inhibitor of the T type calcium channels in the pancreatic beta cells.

In view of the foregoing, applicant maintains that the claims are enabled, and respectfully requests that the rejection under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

35 U.S.C. §102 Rejections

On page 27 of the Office Action, the Examiner rejected claims 43 and 47 under 35 U.S.C. §102(b) as allegedly anticipated by Verma et al. (Cardiovascular Research 34:121-128, 1997). The Examiner stated that "Verma, S. et al. disclose a method wherein hypertensive rats are administered mibefradil, a T-type calcium channel blocker, with a resultant

decrease in insulin secretion, which would necessarily be a decrease in insulin secretion by the rat beta cells." Applicant respectfully traverses this rejection.

The claims herein are directed to a method of modifying insulin secretion by pancreatic beta cells by modifying levels of functional T type calcium channels in the pancreatic beta cells. Referring to page 126 of Verma et al., right column, first full paragraph, the authors state that "it is reasonable to suggest that the effects of the drug [mibefradil] on insulin levels were independent of changes in pancreatic insulin release." Thus, Verma et al. explicitly teach away from the subject invention which is based on the discovery that T type calcium channels in pancreatic beta cells directly affect insulin secretion by pancreatic beta cells.

Therefore, applicant maintains that Verma et al. does not teach or suggest, much less render anticipated, the claims herein. Accordingly, applicant respectfully requests that this rejection be reconsidered and withdrawn.

On page 27 of the Office Action, the Examiner also rejected claims 43 and 47 under 35 U.S.C. §102(a) as allegedly anticipated by Bhattacharjee et al. (Endocrinology 138(9):3735-3740, 1997). Without addressing the substantive issues of this rejection, applicant points out that the cited reference is from the September 1997 issue of Endocrinology and is a reference of applicant that was published less than a year before applicant's effective filing date (August 26, 1998). In support of this response, applicant is currently obtaining written verification of the issue release date from the publisher and will provide a declaration by Ming Li upon receipt thereof. The declaration will also verify that the authors of the reference other than Ming Li were not inventors of the subject invention.

Therefore, applicant maintains that the Bhattacharjee et al. reference is not available as prior art against the

subject invention and respectfully requests that this rejection be reconsidered and withdrawn.

On page 27 of the Office Action, the Examiner also rejected claim 43 under 35 U.S.C. §102(b) as allegedly anticipated by Kato et al. (Metabolism 43(11):1395-1400, 1994). The Examiner alleges that Kato et al. disclose "a method wherein neonatal rats are treated with streptozocin, increasing the level of functional T-type calcium channels, evidenced by the increased Ba^{2+} induced currents, and increasing insulin secretion." Applicant respectfully traverses this rejection.

The claims herein are directed to a method of modifying insulin secretion by pancreatic beta cells by modifying levels of functional T type calcium channels in the pancreatic beta cells. Referring to page 1398 of Kato et al., right column, first full paragraph, the authors are discussing rat pancreatic β cells and conclude that the role of "T-type Ca^{2+} channels in the excitation-secretion coupling of β cells is still unknown." Thus, Kato et al. explicitly teach away from the subject invention which is based on the discovery that T type calcium channels in pancreatic beta cells directly affect insulin secretion by pancreatic beta cells.

Therefore, applicant maintains that Kato et al. does not teach or suggest, much less render anticipated, the claims herein. Accordingly, applicant respectfully requests that this rejection be reconsidered and withdrawn.

Drawings

Applicant has reviewed the Notice of Draftperson's Patent Drawing Review included with the Office Action. In accordance with MPEP §608.02(b), applicant will provide new, corrected drawings after a notice of allowance is issued for this application.

In view of the above amendments and remarks, applicant maintains that the claims as amended herein define patentable subject matter. A notice of allowance is therefore requested. Should any issues remain which can usefully be discussed by telephone, the Examiner is invited to contact applicant's undersigned attorney at the number provided.

Respectfully submitted,

March 12, 2001
Date

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below.

3-12-01
Date

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